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# Genome-wide analysis identifies pleiotropic genes shared between severe mental disorders and biomarkers of cellular aging

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Severe mental disorders such as bipolar disorder (BD), major depressive disorder (MDD) and schizophrenia (SZ) are characterized by reduced life expectancy, premature mortality and alterations of aging biomarkers, leading to hypothesize that they might be associated with accelerated cellular aging. We quantified the genetic overlap between severe mental disorders and a comprehensive set of aging biomarkers including multivariate longevity and healthy aging (mvAge), brain age gap (BAG), leucocyte telomere length (gLTL), mitochondrial DNA copy number and epigenetic age acceleration (gEAA) using cutting-edge methods, and evaluated their functional enrichment and suitability as drug targets. All disorders were negatively correlated with mvAge. Further, MDD correlated negatively with gLTL and positively with gEAA. We identified several pleiotropic variants, with nine genes (*AC068490.2*, *ASIC2*, *CNNM2*, *FURIN*, *GPM6A*, *HS6ST3*, *RP5-1043L13.1*, *SORCS3* and *SP4*) containing variants shared between aging biomarkers and all disorders. Functional analyses with summary-data-based Mendelian randomization showed that increased expression of the druggable gene *CRHR1* in the prefrontal cortex was associated with increased risk of MDD and BAG measures. Our findings suggest that shared heritability might contribute to reduced longevity and healthy aging in severe mental disorders and identify pleiotropic genes involved in synaptic function and metabolic processes related to micronutrients such as folate and magnesium.

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## INTRODUCTION

Severe mental disorders such as bipolar disorder (BD), major depressive disorder (MDD) and schizophrenia (SZ) are characterized by a reduced life expectancy and premature mortality up to 10–20 years compared with the general population [1]. In addition, people living with mental disorders show alterations in aging biomarkers such as shorter telomere length (TL) [2], altered mitochondrial DNA copy number (mtDNA-cn) [3], accelerated epigenetic aging [4] and changes in brain structures that are usually associated with aging [5]. These findings led to hypothesize the association of severe mental disorders with accelerated cellular aging, a condition in which the rate of cellular aging is faster compared with chronological aging [6]. Several aging hallmarks have been described [7]. Telomeres are specialized DNA-protein structures located at the ends of chromosomes that play a crucial role in ensuring chromosome stability [7]. With each cell division, telomeres undergo a progressive shortening that ultimately induces cell senescence or apoptosis. This physiological shortening can be accelerated by different biological stressors, such as inflammation and oxidative stress. Consistently, shorter TL is considered a marker of cellular senescence and has been associated with increased all-cause mortality risk [8]. Recent meta-analyses support an association between shorter TL and severe mental disorders [9], with leukocyte telomere length (LTL) being the most investigated biomarker. Mitochondrial function deteriorates with age due to accumulation of mtDNA mutations, limited DNA repair capacity and alterations in the respiratory chain complexes, leading to increased production of reactive oxygen species and permeabilization of mitochondrial membrane [7]. The mtDNA-cn, that is a measure of the abundance of mitochondrial genomes per cell, is an indirect biomarker of mitochondrial function and has been suggested to decline with age [10]. While a lower mtDNA-cn has been associated with poorer outcomes and higher all-cause mortality [11], the association between mtDNA-cn and mental disorders appears to be complex. In fact, while a reduced mtDNA-cn has been reported in people living with severe mental disorders by some studies [12], other studies, conversely, reported higher mtDNA-cn in people living with mental disorders compared to controls [13] or a reduction in mtDNA-cn during remission compared with the acute phase of MDD [14]. Epigenetic changes are also highly investigated aging hallmarks [7]. Research has focused on epigenetic clocks, i.e. tools that use machine

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learning models to analyze patterns of DNA methylation at selected sites to predict life expectancy or the risk of developing age-associated diseases [15]. These clocks allow to compute epigenetic age acceleration (EAA), that is the discrepancy between an individual's biological age estimated by epigenetic clocks and chronological age, with a higher EAA indicating faster biological aging. People living with severe mental disorders show higher EAA compared with controls [16–18], with some studies indicating significant associations with symptom severity [16], cognitive impairment [18] or suicide [19]. Most aging hallmarks are measured in peripheral tissues, often as a proxy to the brain and with obvious limitations, but recent studies are also focusing on aging hallmarks which are directly measured in the brain and that therefore have a potentially higher relevance for the functions of the central nervous system. Indeed, during aging the brain may show alterations such as reductions in gray and white matter, enlargement of the ventricles, as well as disrupted neuroplasticity, network activity and neuronal calcium homeostasis [20]. Similarly to other molecular measures, it is therefore possible to compute a brain age gap (BAG), that is the difference between brain age predicted using magnetic resonance imaging scans and chronological age of an individual. To this regard, people living with severe mental disorders show abnormalities in structural and functional connectivity, as well as a higher BAG compared with controls [21].

While several studies indicate that people living with severe mental disorders carry biological signatures of accelerated cellular aging, little is known on the temporal association, i.e. whether accelerated aging anticipates the mental disorder, represents a consequence or is partly linked to shared genetic factors. Both mental disorders and aging biomarkers have a genetic component that interacts with environmental factors. Genome-wide association studies (GWAS) based on large international efforts such as the Psychiatric Genomics Consortium (PGC) have identified several single nucleotide polymorphisms (SNP) involved in severe mental disorders [22–24]. While fewer studies have investigated the genetic bases of aging hallmarks, genome-wide significant SNPs have been identified for aging-related traits such as a multivariate GWAS of aging (mvAge, based on measures related to longevity and healthy aging) [25], BAG measures [26], LTL [27], mtDNA-cn [28] and EAA [29]. Recent studies support the hypothesis that shared genetic factors might underlie at least part of the association observed between severe mental disorders and accelerated cellular aging. Mutz and Lewis reported a polygenic risk score for MDD but not anxiety disorders or BD to be associated with shorter telomeres [30]. Muntané and colleagues used the conjunctional false discovery rate (conjFDR) method to evaluate the cross-trait pleiotropy between SZ or BD and genetically predicted human parental lifespan (gPLS) as a surrogate of life expectancy [31]. The authors identified 39 and 8 loci shared between gPLS and SZ or BD, respectively, with mixed directions of effect [31]. Other studies used two-sample mendelian randomization (MR) to estimate potential causal relationships between mental disorders and markers of aging. Luo and colleagues reported MDD to be associated with genetically predicted EAA (gEAA) using the GrimAge epigenetic clock [32], as well as with shorter genetically predicted LTL (gLTL) [32]. A subsequent study reported a significant association between BD, but not MDD, and higher GrimAge gEAA [33]. While these approaches support the potential role of genetic factors in the accelerated cellular aging observed in mental disorders, which specific genetic loci or SNPs might be involved is still largely unexplored. In a recent study, we used the conjFDR method to identify for the first time genetic variants shared between severe mental disorders and two aging hallmarks (gLTL and genetically predicted mtDNA-cn [g-mtDNA-cn]) [34]. Since different aging hallmarks offer information on distinct aspects of biological aging, it is crucial to obtain a comprehensive picture of determinants shared between severe mental disorders and a comprehensive set of aging biomarkers, including the multivariate longevity GWAS mvAge, BAG measures based on grey matter (BAG-GM), white matter (BAG-WM), grey and white matter (BAG-GWM) and EAA. In the present study we quantified the genetic overlap and dissected genetic determinants shared between severe mental disorders and a comprehensive array of aging hallmarks using an array of cutting-edge methods such as bivariate causal mixture models and conjFDR. We also conducted an in-silico evaluation of the functional enrichment and druggability of identified loci and used two-sample MR to evaluate potential causal relationships between mental disorders and markers of aging. Finally, we applied summary-data-based mendelian randomization (SMR) with expression (eQTL) and methylation (mQTL) quantitative trait loci analysis to identify pleiotropic genes associated with mental disorders and aging biomarkers via changes in gene expression or methylation in brain data. Our results provide a comprehensive picture of shared genetic bases between severe mental disorders and markers of biological aging.

## MATERIALS AND METHODS

### GWAS datasets

We conducted cross-trait analyses using the largest publicly available releases of GWAS summary statistics for BD, MDD and SZ and for nine markers of biological aging. To avoid sample overlap, for BD, MDD and SZ we used the GWAS summary statistics excluding participants from UK Biobank. The BD sample included up to 57,833 cases and 722,909 controls [22], the MDD sample 357,636 cases and 1,281,936 controls [23], while the SZ sample 53,386 cases and 77,258 controls [24], all of European origin. Summary statistics for a multivariate longevity and healthy aging GWAS (mvAge), including around 1.9 million participants of European ancestry, were modelled by Rosoff and colleagues with genomic SEM based on five GWASs encompassing life expectancy (parental lifespan and extreme longevity), EAA and healthy aging (healthspan and frailty) [25]. GWAS data on three BAG measures derived from grey matter (BAG-GM), white matter (BAG-WM) or both gray and white matter (BAG-GWM) were obtained for 54,890 participants from UK Biobank [26]. BAGs are calculated based on the difference between an individual's chronological age and machine learning predicted brain age from magnetic resonance imaging data. GWAS summary statistics for gLTL [27] and for mtDNA-cn (ascertained using the AutoMitoC pipeline, which leverages SNP array probe intensities) [28] were obtained for 472,174 and 383,476 UK Biobank participants, respectively. Finally, summary statistics for EAA based on one first-generation (intrinsic EAA [IEAA]) and two second-generation epigenetic clocks (GrimAge and phenoage) were available for 34,710 participants of European ancestry, from different cohorts [29]. For all GWAS datasets, ethical approval was obtained by the original GWAS studies and quality control procedures, including adjustment for population stratification, were performed by the original studies. For all analyses except SMR, strand ambiguous variants (A/T and C/G) or variants located in regions characterized by strong LD such as the Major Histocompatibility Complex (MHC) region (chr6:25,119,106-33,854,733), chromosome 8p23.1 (chr8:7,200,000–12,500,000) and the *MAPT* gene (chr17:40,000,000–47,000,000) were excluded and analyses were conducted on autosomal SNPs shared between each couple of traits.

### Global genetic correlation analysis

Cross-trait global genetic correlation analysis was conducted using LDSC [35]. This method allows to study the genetic correlation considering the average of the shared signals across the genome, including the contribution of SNPs that do not reach genome-wide significance and considering sample overlap and population stratification. Linkage disequilibrium scores were computed using 1000 Genomes European data. Intercepts of genetic covariance and relative standard errors (se) estimated by LDSC were computed to estimate potential sample overlap and are reported in Supplementary Table 1. A Bonferroni correction was applied based on the number of genetic correlations tested and a $p < 0.00076$ (i.e. 0.05/66) was considered to be significant.

### Bivariate causal mixture models (MiXeR)

We used bivariate causal mixture models (MiXeR, v. 1.3) to quantify the genetic overlap between mental disorders and each aging phenotype by estimating the total number of shared and trait-specific genetic variants [36]. First, we constructed conditional QQ plots, i.e. modified

versions of the standard QQ plots that allow to visualize the cross-trait polygenic enrichment. These plots are constructed by creating subsets of SNPs based on the level of association with the secondary phenotype (using three thresholds $p \leq 0.10$, $p \leq 0.01$ and $p \leq 0.001$). Under cross-trait polygenic enrichment, p-values show progressive leftward deflections. We applied causal mixture models to quantify the genetic overlap between mental disorders and aging phenotypes. For each trait, we computed univariate estimates to estimate the number of trait-influencing loci. Next, we computed bivariate estimates of genetic overlap. Additive genetic effects are modeled as a mixture of components that are plotted in Venn diagrams and that represent SNPs not associated with any of the two traits, with only one trait or with both. Dice coefficients (DC), that represent the proportion of SNPs shared between two traits out of the total number of SNPs estimated to be associated with both traits, are reported. In addition, we computed the percentages of SNPs shared between two traits out of the number of SNPs associated with the primary or secondary trait, respectively. The fit of MiXeR models was evaluated based on the best vs min and best vs max AIC values.

### Conditional and conjunctional false discovery rate analysis

To identify shared loci between mental disorders and markers of biological aging, we computed conjFDR with pleioFDR [37]. conjFDR is a Bayesian method that allows to identify genetic loci simultaneously associated with two traits, thus representing an approach complementary to causal mixture models. Briefly, the conditional false discovery rate (condFDR) method computes GWAS statistics in a primary trait (e.g. BD) by leveraging pleiotropic enrichment with a GWAS in a secondary trait (e.g. BAG-GM). For each p-value in the primary trait, a condFDR value is estimated by computing the stratified empirical cumulative distribution function of the p-values. After inverting the primary and secondary traits, the conjFDR is defined as the maximum of the two condFDR values. A conjFDR value < 0.05 was considered significant, as in previous studies [38].

### Functional enrichment and identification of druggable targets

Independent genetic loci shared between two traits were defined according to the FUMA protocol [39]. Briefly, lead SNPs were defined by a clumping of SNPs significant and independent at $r^2 < 0.6$, and a secondary clumping at $r^2 < 0.1$, while loci separated by a distance lower than 250 kb were merged [39]. For significant lead SNPs, the direction of effect was evaluated based on the effect sizes (beta [β]) reported in the original GWAS. Functional annotation of significant SNPs was performed using the CADD score, which predicts how deleterious a variant is on protein structure/function and the RegulomeDB rank (based on known and predicted regulatory elements including regions of DNase hypersensitivity, binding sites of transcription factors and promoter regions, ranging from 1 to 7 with 1 being associated with highest evidence of functional effects) in FUMA [39]. Functional enrichment analyses were conducted on genes in which SNPs were shared between mental disorders and aging biomarkers with the direction of effect expected based on the hypothesis of accelerated cellular aging (i.e. SNPs in which the allele associated with increased risk of mental disorders was negatively associated with mvAge, gLTL or g-mtDNA-cn, or positively with genetically predicted brain age gap [gBAG] or gEAA). Functional enrichment for KEGG pathways or gene ontology (GO) terms was conducted with WebGestalt [40], adjusting results based on FDR. We used STRING to investigate whether proteins encoded by the identified genes showed a significant PPI enrichment [41]. Pleiotropic SNPs were visualized in a Circos plot with the circlize R package. A significant PPI enrichment indicates that the identified proteins are predicted to have more interactions among themselves than would be expected for a set of proteins of the same size randomly drawn from the genome. This analysis was conducted using all interaction sources, restricted to a 'high confidence' minimum required interaction score. Druggability of these genes was investigated using DGIdb [42]. In this database, genes are defined as 'druggable' based on their involvement in selected pathways, molecular functions or gene families according to information retrieved from different drug target repositories, such as DrugBank, PharmGKB, Chembl, Drug Target Commons and others.

### Investigation of causal relationships between mental disorders and aging biomarkers

Pair-wise associations between mental disorders and aging biomarkers were tested with two-sample MR using the TwoSampleMR and the ieugwasr R packages [43]. MR uses genetic variants as instrumental variables (IV) to analyze the causal effect of exposure on an outcome. To evaluate the direction of the association, the MR analysis was repeated twice for each pair of mental disorders and aging biomarkers, considering each trait to be the exposure or the outcome alternatively. IVs were selected based on the association with the exposure at a genome-wide significant threshold ($p < 5.0E-8$) and clumped using European data from the IEU GWAS database. Exposure and outcome data were harmonized and palindromic SNPs removed using the ieugwasr R package. The presence of horizontal pleiotropy was checked based on the evaluation of the intercept term in MR Egger regression, and the global test implemented in the mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) R package. MR analyses were conducted with five widely used methods implemented in the ieugwasr package: IVW, MR-Egger regression, weighted median, weighted mode and simple mode. In addition, we computed raw and outlier corrected estimates with the MR-PRESSO test and conducted a sensitivity analysis using MRlap [44]. This method provides MR estimates accounting for different bias, such as potential sample overlap and use of weak instruments [44]. For couples of traits showing a significant association based on different methods, and confirmed by the sensitivity analysis conducted with MRlap, we reported SNP specific statistical values for all SNPs associated with the exposure (beta, se, p values and F-statistics computed as $beta^2_x$ / $se^2_x$, where beta and se represent the SNP-exposure effect estimate and standard error of the beta, respectively, for each SNP $x$) [45]. An F-statistic > 10 was considered to indicate adequate instrument strength as previously suggested [46]. Finally, we performed a leave-one-out analysis, leaving out each SNP in turn, to identify if a single SNP was driving the association. A Bonferroni correction was applied based on the number of pairs of phenotypes tested and a $p < 0.0009$ (i.e. 0.05/54) was considered to be significant.

### Integrative analysis of GWAS and molecular quantitative trait locus data

We used SMR to identify genes associated with mental disorders and aging biomarkers via changes in gene expression in brain regions [47]. eQTL data were obtained from the PsychENCODE project (including RNA-seq data from 1387 prefrontal cortex samples) [48] and the BrainMeta v.2.0 study (including RNA-sequencing data from 2865 brain cortex samples from 2443 unrelated individuals of European origin) [49]. After the identification of pleiotropic genes, we conducted the SMR analysis to identify methylation probes associated with the traits of interest in the same loci. mQTL data were obtained from the Brain-mMeta meta-analysis, including methylation data from around 1160 adult cortex or fetal brain samples [50]. For each dataset, a Bonferroni correction was applied based on the number of probes. Finally, for significant probes and genes identified in the previous step, the SMR analysis was conducted with methylation as the exposure and gene expression as the outcome. For this analysis, a multiple testing correction based on Bonferroni was applied based on the number of analyzed probes and gene pairs ($n = 42$). We analyzed cis-QTLs with default options. The heterogeneity in dependent instruments (HEIDI) test was used to identify violations of the assumptions of MR and a threshold of $p = 0.01$ was considered to be significant, as previously suggested [51].

## RESULTS

### Global genetic correlation analysis

Supplementary Figure 1 shows the results of the global genetic correlation analysis. All severe mental disorders were significantly negatively correlated with mvAge (BD: $r_g = -0.13$, se = 0.02, $p = 2E-08$; MDD: $r_g = -0.53$, se = 0.02, $p = 1.6E-143$; SZ: $r_g = -0.08$, se = 0.02, $p = 9.6E-05$). In addition, MDD was significantly negatively correlated with gLTL ($r_g = -0.14$, se = 0.02, $p = 1.4E-10$) and positively correlated with GrimAge gEAA ($r_g = 0.23$, se = 0.05, $p = 5.7E-07$).

### Bivariate causal mixture models

Results from bivariate causal mixture model analyses are reported in Table 1, while the Venn diagrams showing shared heritability between BD, MDD or SZ and aging biomarkers are shown in Fig. 1. Conditional QQ plots (Supplementary Figures 2–4) suggested

**Table 1.** Bivariate causal mixture models analysis between severe mental disorders and aging biomarkers.

| Trait1 | Trait2 | Dice, mean (sd) | % variants shared with aging markers among those associated with mental disorders | % variants shared with mental disorders among those associated with aging markers | Best vs min AIC | Best vs max AIC |
|---|---|---|---|---|---|---|
| BD | mvAge | 0.73 (0.05) | 82.25% | 66.20% | 31.28 | 2.07 |
| BD | gBAG-GM | 0.25 (0.05) | 15.98% | 59.89% | 5.53 | 2.06 |
| BD | gBAG-WM | 0.21 (0.04) | 13.33% | 47.82% | 2.87 | 5.59 |
| BD | gBAG-GWM | 0.24 (0.05) | 15.58% | 56.12% | 4.16 | 3.77 |
| BD | gLTL | 0.04 (0.01) | 2.12% | 44.01% | 5.41 | 6.83 |
| BD | g-mtDNA-cn | 0.02 (0.01) | 1.00% | 38.94% | 2.23 | 7.24 |
| BD | GrimAge gEAA | 0.14 (0.04) | 7.55% | 71.71% | -0.13 | -0.78 |
| BD | IEAA gEAA | 0.06 (0.01) | 2.87% | 77.18% | -0.20 | 2.34 |
| BD | Phenoage gEAA | 0.01 (0.01) | 0.46% | 23.84% | -0.52 | 0.93 |
| MDD | mvAge | 0.91 (0.03) | 84.39% | 99.37% | 42.90 | -0.07 |
| MDD | gBAG-GM | 0.15 (0.06) | 8.76% | 48.02% | 0.55 | 2.76 |
| MDD | gBAG-WM | 0.24 (0.04) | 14.23% | 74.66% | 11.51 | 1.51 |
| MDD | gBAG-GWM | 0.23 (0.04) | 13.44% | 70.84% | 5.45 | 1.64 |
| MDD | gLTL | 0.06 (0.00) | 3.05% | 92.78% | 2.50 | 2.40 |
| MDD | g-mtDNA-cn | 0.01 (0.01) | 0.43% | 24.46% | 2.29 | 6.66 |
| MDD | GrimAge gEAA | 0.13 (0.03) | 7.11% | 98.86% | -1.71 | -1.72 |
| MDD | IEAA gEAA | 0.02 (0.01) | 0.96% | 37.57% | 1.92 | 3.92 |
| MDD | Phenoage gEAA | 0.03 (0.00) | 1.29% | 99.23% | -1.94 | -1.79 |
| SZ | mvAge | 0.78 (0.06) | 77.22% | 78.08% | 54.76 | 4.91 |
| SZ | gBAG-GM | 0.27 (0.04) | 19.32% | 76.24% | 3.83 | 0.95 |
| SZ | gBAG-WM | 0.23 (0.03) | 13.75% | 61.95% | 4.61 | 3.80 |
| SZ | gBAG-GWM | 0.24 (0.03) | 14.78% | 66.91% | 3.13 | 2.11 |
| SZ | gLTL | 0.04 (0.01) | 2.13% | 55.51% | 6.76 | 8.97 |
| SZ | g-mtDNA-cn | 0.01 (0.01) | 0.55% | 26.74% | 2.89 | 7.31 |
| SZ | GrimAge gEAA | 0.07 (0.05) | 3.78% | 45.05% | -0.36 | -0.09 |
| SZ | IEAA gEAA | 0.04 (0.01) | 2.24% | 75.75% | 1.64 | 2.05 |
| SZ | Phenoage gEAA | 0.01 (0.00) | 0.64% | 42.18% | -0.78 | 1.08 |

Models with negative values for the best vs min AIC and the best vs max AIC are considered not reliable.
*AIC*, Akaike information criterion; *BD*, bipolar disorder; *gBAG-GM*, genetically predicted brain age gap gray matter; *gBAG-GWM*, genetically predicted brain age gap gray white matter; *gBAG-WM*, genetically predicted brain age gap white matter; *gEAA* genetically predicted epigenetic age acceleration; *IEAA*, intrinsic epigenetic age acceleration; *gLTL*, genetically predicted leukocyte telomere length; *g-mtDNA-cn*, genetically predicted mitochondrial DNA copy number; *MDD*, major depressive disorder; *mvAge*, multivariate GWAS of aging; *sd*, standard deviation; *SZ*, schizophrenia.

relevant cross-trait pleiotropy for most analyzed pairs of traits, though we observed differences in the percentage of shared genetic heritability and in the polygenicity of the analyzed traits (Table 1, Fig. 1 and Supplementary Figure 5). mvAge showed the highest shared heritability with mental disorders, with dice coefficients ranging from 0.73 for BD to 0.91 for MDD. Based on the AIC values, most MiXeR models provided relevant information compared to a model assuming minimum or maximum pleiotropy, but models including EAA often showed poor performance. Specifically, the models including GrimAge gEAA showed a poor fit based on the AIC values for all disorders, while IEAA gEAA showed an acceptable fit only for MDD and SZ. In addition, the model including MDD and mvAge did not perform better than a model that would consider a maximum pleiotropic overlap (Table 1). A high proportion of variants associated with mental disorders were also associated with mvAge (from 77.2% for SZ to 84.4% for MDD), but only a small proportion with other aging markers (around 10–15% for BAG measures and 2–3% for gLTL, Fig. 2 and Table 1). On the other hand, a large proportion of variants associated with aging markers was also associated with mental disorders (e.g. from 47 to 74% for BAG-measures, Fig. 1 and Table 1).

### Identification of shared genetic loci with conjFDR

Figure 2 shows the number of significant genetic variants (conjFDR < 0.05) shared between each mental disorder and aging biomarker showing the expected or opposite direction of effect under the hypothesis of accelerated cellular aging in mental disorders. The complete lists of significant genetic variants and genomic loci are reported in Supplementary Tables 2–8 for BD, Supplementary Tables 9–15 for MDD and Supplementary Tables 16–22 for SZ. In accordance with causal mixture model results, mvAge shared the highest number of genetic variants with all disorders, followed by gLTL and gBAG measures (Fig. 2), while only a limited number of shared genetic variants were identified for g-mtDNA-cn or gEAA. MDD shared the highest number of genetic variants with aging biomarkers, followed by SZ and BD, although SZ shared a higher number of variants with BAG

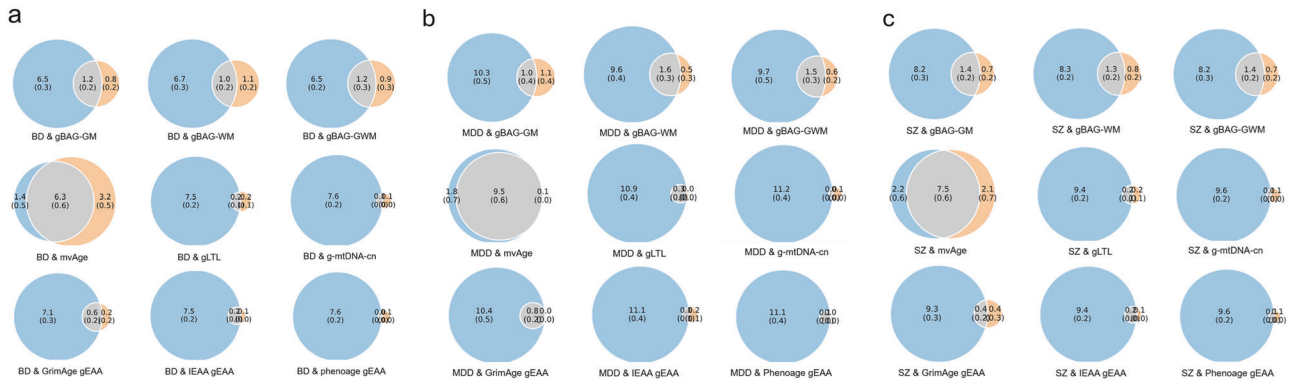


**Fig. 1 Bivariate causal mixture models between mental disorders and aging biomarkers.** Venn diagrams for BD (**a**), MDD (**b**) and SZ (**c**) showing the estimated number of causal variants (in thousands), explaining 90% of heritability for mental disorders (on the left) and biomarkers of aging (on the right). Shared variants are colored in gray, variants specific for mental disorders in blue, while variants specific for biomarkers of aging in orange. The size of the circles is proportional to the degree of polygenicity of each trait. Abbreviations: BD, bipolar disorder; gBAG-GM, genetically predicted brain age gap gray matter; gBAG-GWM, genetically predicted brain age gap gray white matter; gBAG-WM, genetically predicted brain age gap white matter; gEAA, genetically predicted epigenetic age acceleration; IEAA, intrinsic epigenetic age acceleration; gLTL, genetically predicted leukocyte telomere length; g-mtDNA-cn, genetically predicted mitochondrial DNA copy number; MDD, major depressive disorder; mvAge, multivariate GWAS of aging, SZ, schizophrenia.

measures, g-mtDNA-cn or EAA compared with MDD. In the case of MDD, most variants shared with mvAge and LTL showed the expected direction of effect based on the hypothesis of accelerated cellular aging, while for BD and SZ we observed a mixed pattern of effect direction (Fig. 2).

Genes containing variants shared between BD and any aging biomarker with the expected direction of effect were enriched for the "pteridine-containing compound metabolic process" biological process GO term and for the two KEGG pathways "One carbon pool by folate" and "antifolate resistance" (Supplementary Table 23), while genes containing variants shared between MDD and any aging biomarker were enriched for several GO terms related to neural function and synapses, the most significant of which were "neural projection guidance", "synapse organization" and "regulation of synapse structure or activity" (Supplementary Table 24). Genes containing variants shared between SZ and any aging biomarker were enriched for a smaller number of terms related to synapses as well as the "metal ion transmembrane transporter activity" molecular function GO term (Supplementary Table 25).

Proteins encoded by genes shared between BD ($p = 0.002$, Supplementary Figure 5d), MDD ($p = 0.003$, Supplementary Figure 5e) or SZ ($p = 0.035$, Supplementary Figure 5f) and aging biomarkers showed a significant protein-protein interaction (PPI) enrichment. Table 2 shows genes containing genetic loci shared between more than one mental disorder and aging biomarkers (Table 2). Nine genes contained variants shared between aging markers and all three mental disorders, 14 between aging markers, MDD and SZ, 11 between aging markers, BD and MDD and two between aging markers, BD and SZ (Table 2). Most of the cross-disorder genes were associated with mvAge, while other genes with BAG measures (*ANK3*, *CCDC91*, *FADS2*, *TFR2*, *TRPS1* and *ZNF536*) or LTL (*CNNM2*, *FURIN* and *SORCS3*). Of these cross-disorder genes, six are part of the druggable genome based on DGIdb (Table 2).

## Investigation of causal relationships between mental disorders and aging biomarkers

Analyses evaluating the presence of horizontal pleiotropy are reported in Supplementary Table 26. For BD, only nominal associations were detected (Supplementary Table 27). Conversely, we observed a significant negative bidirectional association between MDD and mvAge. The association between mvAge (exposure) and MDD (outcome) was supported by the inverse-variance weighted (IVW, beta = −0.68, p = 3.8E-05), weighted median (beta = −0.51, p = 1.8E-04), MR-PRESSO raw (beta = −0.77, p = 5.2E-05) and MR-PRESSO outlier-corrected (beta = −0.73, p = 4.5E-06) methods, as well as by the sensitivity analysis conducted with MRlap (beta = −0.37, p = 2.0E-06, Supplementary Table 28). A causal association between MDD (exposure) and mvAge (outcome) was supported by all methods at a multiple testing significant threshold and by the MR Egger method at a nominally significant threshold (Supplementary Table 28). The sensitivity analysis conducted with MRlap also showed a significant association (beta = −0.24, p = 2.0E-24). For both analyses, all IVs showed F-statistics > 10 (Supplementary Table 29) and we detected evidence of horizontal pleiotropy based on MR-PRESSO but not MR Egger (Supplementary Table 26). Leave-one-out analyses showed that the estimates remained significant after exclusion of each SNP, indicating that no single IV drove the observed association (Supplementary Table 30).

While we detected a significant association between MDD and gLTL with the weighted median (beta = −0.05, p = 1.0E-04) and MR-PRESSO outlier corrected methods (beta = −0.05, p = 1.6E-05, Supplementary Table 28), the sensitivity analysis conducted with MRlap was only nominally significant (beta = −0.12, p = 6.0E-03). Finally, while a significant association between MDD and GrimAge gEAA with the IVW (beta = 0.56, p = 4.8E-04) method was detected, this result was not supported by the sensitivity analysis (Supplementary Table 28). Finally, for SZ only nominally significant associations were detected (Supplementary Table 31).

## Integrative analysis of GWAS and molecular quantitative trait locus data

Results from the SMR analysis highlighting genes associated with both mental disorders and aging markers via changes in gene expression in brain data, with the expected or opposite direction of effect, are shown in Table 3 and Supplementary Table 32, respectively. Increased predicted expression of *C12orf65* and *OGFOD2*, as well as reduced expression of *CDK2AP1* and *RP11-282O18.3* was associated with increased risk of SZ and gLTL (Fig. 3). In addition, reduced methylation of two probes located in the same locus in chromosome 12 (cg07899411 and cg09931783) was associated with increased risk of SZ and reduced gLTL. Consistently, methylation of these two probes was associated with reduced predicted expression of the *OGFOD2* gene (Table 3). For other loci, the SMR analysis suggested a pleiotropic association of loci via altered gene expression but not methylation levels.

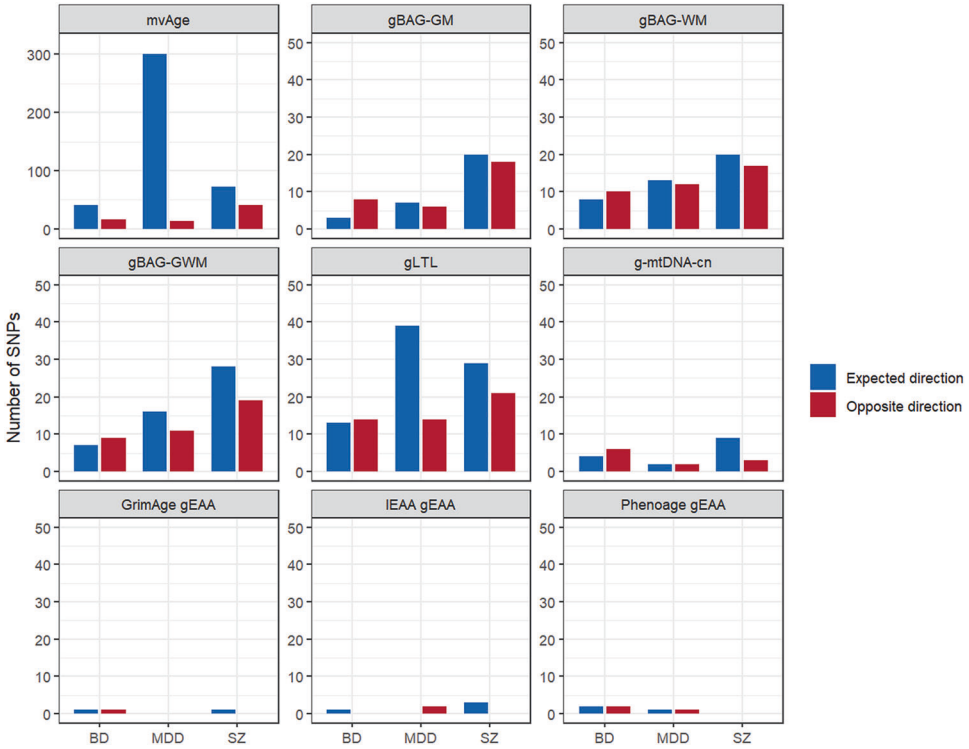


**Fig. 2 Number of significant genetic variants shared between mental disorders and aging biomarkers showing the expected or opposite direction of effect based on the hypothesis of accelerated cellular aging in mental disorders.** Abbreviations: gBAG-GM, genetically predicted brain age gap gray matter; gBAG-GWM, genetically predicted brain age gap gray white matter; gBAG-WM, genetically predicted brain age gap white matter; BD, bipolar disorder; gEAA, genetically predicted epigenetic age acceleration; gLTL, genetically predicted leukocyte telomere length; g-mtDNA-cn, genetically predicted mitochondrial DNA copy number; MDD, major depressive disorder; mvAge, multivariate GWAS of aging; SZ, schizophrenia.

Namely, increased expression of *RNF123* was associated with increased risk of MDD, and negatively associated with mvAge and gLTL, while increased expression of *PPP6C* with increased risk of MDD, increased gBAG-GM and gBAG-GWM (Supplementary Figure 6). Reduced expression of *CRHR1* was associated with reduced risk of MDD and reduced gBAG-GM, gBAG-WM and gBAG-GWM. Finally, reduced expression of *FTCDNL1* was associated with increased risk of SZ, increased gBAG-GM and gBAG-GWM (Fig. 3).

## DISCUSSION

Using the largest available GWAS summary statistics, we identified several loci shared between mental disorders and aging biomarkers. The most robust associations were observed for the mvAge construct, representative of longevity and healthy aging, as this trait was significantly negatively correlated with all three severe mental disorders using global genetic correlation and also showed the highest amount of genetic overlap, suggesting that genetic factors may contribute to the premature mortality observed in individuals with severe mental disorders. MDD showed the highest number of pleiotropic loci. For this disorder, most identified loci (especially those shared with mvAge and gLTL) showed the expected direction of effect based on the hypothesis of accelerated cellular aging. Conversely, for BD and SZ a high percentage of shared genetic variants showed an opposite direction of effect. This mixed pattern of effect direction has been previously observed by studies investigating shared genetic bases between mental disorders and related phenotypes, such as intelligence [52], metabolic [53], and cardiovascular [54] phenotypes, as well as by a previous study exploring shared heritability between SZ or BD and genetically predicted parental lifespan [31]. This might lead to speculate that only specific subgroups of individuals with these disorders might be at risk of accelerated cellular aging, while others might be protected, as supported by findings from Spano et al., which identified a cluster of mostly BD individuals with young age and accelerated aging [55]. Compared to a previous study that identified 39 loci shared between SZ and genetically predicted parental lifespan [31], our cross-trait analysis between SZ and mvAge replicated 13 genes and identified several novel shared loci (Supplementary Table 16). As for our cross-trait analysis between BD and mvAge, it identified 56 loci compared with the eight identified by the previous study and replicated the one located in the *SYNE1* gene (Supplementary Table 2).

Most of the identified pleiotropic variants were specifically shared between mental disorders and each aging biomarker. More in detail, only a minority of the genes associated with BAG measures were also associated with peripheral aging biomarkers via different SNPs, and our global genetic correlation analysis suggested distinct heritability for most groups of aging biomarkers (Fig. 1). Thus, while deeply interconnected with each other [7], different aging biomarkers may reflect distinct aspects of accelerated cellular aging.

Functional enrichment analyses suggest that proteins encoded by pleiotropic genes identified in this study interact with each other. Loci shared between MDD or SZ and any aging biomarker were enriched for several GO terms related to synaptic function and to the central nervous system development (Supplementary Tables 24 and 25). Indeed, aging exerts a substantial impact on synaptic plasticity, having been associated with structural and functional synaptic plasticity alterations [56]. A recent single-nucleus RNA sequencing study suggested that people with SZ and people of advanced age show reduced expression levels of synapse-related genes in either

**Table 2.** Genes containing genetic loci shared between aging markers and more than one mental disorder.

| Gene | CHR | BD and aging | MDD and aging | SZ and aging | Druggable gene |
|---|---|---|---|---|---|
| *AC004053.1* | 4 | – | mvAge | mvAge | No |
| *AC068490.2* | 2 | mvAge | mvAge | mvAge | No |
| *ANK3* | 10 | – | gBAG-WM | gBAG-WM | No |
| *ASIC2* | 17 | mvAge | mvAge | mvAge | Yes |
| *CCDC91* | 12 | gBAG-WM, gBAG-GWM, phenoage | gBAG-WM, gBAG-GWM | – | No |
| *CNNM2* | 10 | gLTL | gLTL | gLTL | No |
| *ELAVL4* | 1 | – | mvAge | mvAge | No |
| *EML1* | 14 | mvAge | mvAge | – | No |
| *EYS* | 6 | mvAge | mvAge | – | Yes |
| *FADS2* | 11 | gBAG-GM, gBAG-WM, gBAG-GWM | gBAG-WM, gBAG-GWM | – | No |
| *FOXP2* | 7 | – | mvAge | mvAge | No |
| *FBXL17* | 5 | mvAge | mvAge | – | No |
| *FURIN* | 15 | gLTL | gLTL | gLTL | Yes |
| *GPM6A* | 4 | mvAge | mvAge | mvAge | Yes |
| *HS6ST3* | 13 | mvAge | mvAge | mvAge | No |
| *LINC01122* | 2 | – | mvAge | gLTL, mvAge | No |
| *MAML3* | 4 | mvAge | mvAge | – | No |
| *MED24* | 17 | mvAge | mvAge | – | No |
| *RP11-184D12.1* | 15 | mvAge | mvAge | – | No |
| *RP4-723E3.1* | 20 | mvAge | mvAge | – | No |
| *OSBP2* | 22 | – | mvAge | mvAge | No |
| *PDE4B* | 1 | – | mvAge | mvAge | Yes |
| *RASGRP1* | 15 | – | mvAge | gLTL, mvAge | No |
| *RP5-1043L13.1* | 20 | mvAge | mvAge | mvAge | No |
| *RP5-821D11.7* | 22 | – | gLTL | mvAge | No |
| *SDK1* | 7 | – | mvAge | mvAge | No |
| *SEMA3F* | 3 | mvAge | gBAG-GM | – | Yes |
| *SHANK3* | 22 | g-mtDNA-cn | – | mvAge | No |
| *SORCS3* | 10 | mvAge | gLTL, mvAge | gLTL, mvAge | No |
| *SP4* | 7 | mvAge | mvAge | mvAge | No |
| *TANK* | 2 | mvAge | mvAge | – | No |
| *TCF20* | 22 | – | mvAge | gBAG-WM, gBAG-GWM | No |
| *TFR2* | 7 | gBAG-WM | – | gBAG-WM | No |
| *TRPS1* | 8 | – | gBAG-WM, gBAG-GWM | gBAG-GM, gBAG-WM, gBAG-GWM | No |
| *TTC12* | 11 | – | mvAge | mvAge | No |
| *ZNF536* | 19 | – | gBAG-GM, gBAG-WM, gBAG-GWM, mvAge | gBAG-GM, gBAG-WM, gBAG-GWM | No |

*BD*, bipolar disorder; *CHR*, chromosome; *gBAG-GM*, genetically predicted brain age gap gray matter; *gBAG-GWM*, genetically predicted brain age gap gray white matter; *gBAG-WM*, genetically predicted brain age gap white matter; *gLTL*, genetically predicted leukocyte telomere length; *g-mtDNA-cn*, genetically predicted mitochondrial DNA copy number; *MDD*; major depressive disorder; *mvAge*, multivariate GWAS of aging; *SZ*, schizophrenia.

glutamatergic or GABAergic neurons compared to younger individuals with no SZ [57]. These results, as well as previous studies [58, 59], are in line with our finding of an enrichment of genes involved in synaptic function among those genes containing genetic variants shared between SZ or MDD and markers of cellular aging. This finding also suggests that pleiotropic genes underlying the association between MDD or SZ and cellular aging might be involved in brain relevant functions.

Pleiotropic loci associated with aging biomarkers and BD were enriched for the "pteridine-containing compound metabolic process" biological process GO term and for two pathways related to folate metabolism. Pteridine compounds include, among others, tetrahydrobiopterin (BH4) and folate (vitamin B9). The former represents an essential cofactor for the phenylalanine hydroxylase enzyme and also for the tryptophan hydroxylase enzyme, involved in the first step of the synthesis of serotonin from tryptophan [60]. Release of BH4 has been observed to be

**Table 3.** Integrative analysis of GWAS and molecular quantitative trait locus data.

| SMR analysis of gene expression data | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gene** | **Trait** | **CHR** | **eQTL data** | **topSNP** | **topSNP bp** | **EA/OA** | **Freq EA** | **Beta GWAS** | **Beta eQTL** | **Beta SMR** | **se SMR** | **p SMR** | **HEIDI** | **Adj p SMR** |
| *RNF123* | MDD | 3 | BrainMeta v2 | rs9855505 | 49792158 | T/G | 0.40 | 0.02 | 0.38 | 0.05 | 0.01 | 2.10E-07 | 0.11 | 3.36E-03 |
| *RNF123* | mvAge | 3 | BrainMeta v2 | rs9855505 | 49792158 | T/G | 0.40 | −0.01 | 0.38 | −0.02 | 0.00 | 3.94E-07 | 0.92 | 6.15E-03 |
| *RNF123* | gLTL | 3 | BrainMeta v2 | rs7426497 | 49789814 | G/A | 0.41 | −0.01 | 0.40 | −0.03 | 0.01 | 5.56E-08 | 0.07 | 9.08E-04 |
| *PPP6C* | MDD | 9 | BrainMeta v2 | rs620677 | 127819261 | C/G | 0.31 | −0.02 | −0.49 | 0.04 | 0.01 | 1.67E-07 | 0.96 | 2.67E-03 |
| *PPP6C* | gBAG-GM | 9 | BrainMeta v2 | rs618059 | 127851968 | C/G | 0.22 | −0.12 | −0.58 | 0.20 | 0.04 | 1.17E-06 | 0.40 | 1.90E-02 |
| *PPP6C* | gBAG-GWM | 9 | BrainMeta v2 | rs618059 | 127851968 | C/G | 0.22 | −0.11 | −0.58 | 0.18 | 0.04 | 2.91E-06 | 0.43 | 4.71E-02 |
| *CRHR1* | MDD | 17 | PsychENCODE | rs17577369 | 44192923 | G/A | 0.09 | 0.02 | −0.91 | −0.02 | 0.00 | 3.66E-06 | 0.42 | 3.96E-02 |
| *CRHR1* | gBAG-GM | 17 | PsychENCODE | rs17577369 | 44192923 | G/A | 0.09 | 0.34 | −0.91 | −0.37 | 0.03 | 1.73E-27 | 0.32 | 1.88E-23 |
| *CRHR1* | gBAG-WM | 17 | PsychENCODE | rs17577369 | 44192923 | G/A | 0.09 | 0.48 | −0.91 | −0.53 | 0.04 | 1.33E-40 | 0.26 | 1.45E-36 |
| *CRHR1* | gBAG-GWM | 17 | PsychENCODE | rs17577369 | 44192923 | G/A | 0.09 | 0.44 | −0.91 | −0.49 | 0.04 | 4.81E-39 | 0.22 | 5.23E-35 |
| *FTCDNL1* | SZ | 2 | BrainMeta v2 | rs796364 | 200716119 | C/A | 0.15 | 0.08 | −0.59 | −0.14 | 0.02 | 3.14E-10 | 0.33 | 5.07E-06 |
| *FTCDNL1* | gBAG-GM | 2 | BrainMeta v2 | rs796364 | 200716119 | C/A | 0.15 | 0.15 | −0.59 | −0.26 | 0.05 | 2.06E-07 | 0.28 | 3.33E-03 |
| *FTCDNL1* | gBAG-GWM | 2 | BrainMeta v2 | rs796364 | 200716119 | C/A | 0.15 | 0.13 | −0.59 | −0.22 | 0.05 | 1.53E-06 | 0.49 | 2.48E-02 |
| *C12orf65* | SZ | 12 | BrainMeta v2 | rs11057209 | 123733621 | A/G | 0.44 | 0.07 | 0.33 | 0.22 | 0.04 | 1.0E-08 | 0.17 | 1.7E-04 |
| *C12orf65* | gLTL | 12 | BrainMeta v2 | rs11057209 | 123733621 | A/G | 0.44 | −0.02 | 0.33 | −0.06 | 0.01 | 7.2E-10 | 0.11 | 1.2E-05 |
| *CDK2AP1* | SZ | 12 | PsychENCODE | rs949142 | 123634043 | C/T | 0.68 | −0.07 | 0.27 | −0.24 | 0.05 | 2.8E-06 | 0.63 | 3.1E-02 |
| *CDK2AP1* | gLTL | 12 | PsychENCODE | rs949142 | 123634043 | C/T | 0.68 | 0.02 | 0.27 | 0.07 | 0.01 | 2.4E-07 | 0.89 | 2.7E-03 |
| *OGFOD2* | SZ | 12 | PsychENCODE | rs7957096 | 123544878 | G/A | 0.54 | −0.06 | −0.26 | 0.23 | 0.05 | 4.3E-06 | 0.32 | 4.7E-02 |
| *OGFOD2* | gLTL | 12 | PsychENCODE | rs7957096 | 123544878 | G/A | 0.54 | 0.02 | −0.26 | −0.07 | 0.01 | 3.2E-07 | 0.25 | 3.5E-03 |
| *RP11-282O18.3* | SZ | 12 | PsychENCODE | rs949142 | 123634043 | C/T | 0.68 | −0.07 | 0.32 | −0.21 | 0.04 | 4.9E-07 | 0.34 | 5.4E-03 |
| *RP11-282O18.3* | gLTL | 12 | PsychENCODE | rs949142 | 123634043 | C/T | 0.68 | 0.02 | 0.32 | 0.06 | 0.01 | 1.7E-08 | 0.55 | 1.9E-04 |

**Table 3.** continued

| **SMR analysis of gene expression data** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gene** | **Trait** | **CHR** | **eQTL data** | **topSNP** | **topSNP bp** | **EA/OA** | **Freq EA** | **Beta GWAS** | **Beta eQTL** | **Beta SMR** | **se SMR** | **p SMR** | **HEIDI** | **Adj p SMR** |
| **SMR analysis of methylation data** | | | | | | | | | | | | | | |
| **Probe** | **Trait** | **CHR** | **mQTL data** | **topSNP** | **topSNP bp** | **EA/OA** | **Freq EA** | **Beta GWAS** | **Beta mQTL** | **Beta SMR** | **se SMR** | **p SMR** | **HEIDI** | **Adj p SMR** |
| cg07899411 | SZ | 12 | Brain-mMeta v2 | rs1727300 | 123664205 | T/C | 0.65 | −0.07 | 1.47 | −0.04 | 0.01 | 2.7E-10 | 0.09 | 2.6E-05 |
| cg07899411 | gLTL | 12 | Brain-mMeta v2 | rs1727300 | 123664205 | T/C | 0.65 | 0.02 | 1.47 | 0.01 | 0.00 | 6.2E-14 | 0.04 | 5.9E-09 |
| cg09931783 | SZ | 12 | Brain-mMeta v2 | rs7296418 | 123457619 | T/C | 0.65 | −0.06 | 0.44 | −0.13 | 0.03 | 1.8E-07 | 0.05 | 1.7E-02 |
| cg09931783 | gLTL | 12 | Brain-mMeta v2 | rs7296418 | 123457619 | T/C | 0.65 | 0.02 | 0.44 | 0.04 | 0.01 | 1.8E-09 | 0.02 | 1.7E-04 |
| **SMR analysis of methylation (exposure) and gene expression (outcome)** | | | | | | | | | | | | | | |
| **Probe** | **Gene** | **CHR** | **eQTL-mQTL data** | **topSNP** | **topSNP bp** | **EA/OA** | **Freq EA** | **Beta Out** | **Beta Exp** | **Beta SMR** | **se SMR** | **p SMR** | **HEIDI** | **Adj p SMR** |
| cg07899411 | OGFOD2 | 12 | PsychENCODE, Brain-mMeta v2 | rs1727300 | 123664205 | T/C | 0.65 | −0.18 | 1.47 | −0.12 | 0.03 | 1.9E-06 | 0.01 | 7.9E-05 |
| cg09931783 | OGFOD2 | 12 | PsychENCODE, Brain-mMeta v2 | rs61955214 | 123482424 | C/T | 0.48 | −0.21 | 0.42 | −0.49 | 0.10 | 1.2E-06 | 0.67 | 5.0E-05 |

The table reports results from the SMR analysis for genes or methylation probes significantly associated with mental disorders and aging biomarkers with the expected direction of effect.
*Adj*, adjusted; *bp*, base pair; *CHR*, chromosome; *EA*, effect allele; *eQTL*, expression quantitative trait locus; *Exp*, exposure; *Freq*, frequency; *GWAS*, genome-wide association study; *HEIDI*, heterogeneity in dependent instruments; *mQTL*, methylation quantitative trait locus; *mvAge*, multivariate GWAS of aging; *OA*, other allele; *Out*, outcome; *se*, standard error; *SMR*, summary-data-based Mendelian randomization.

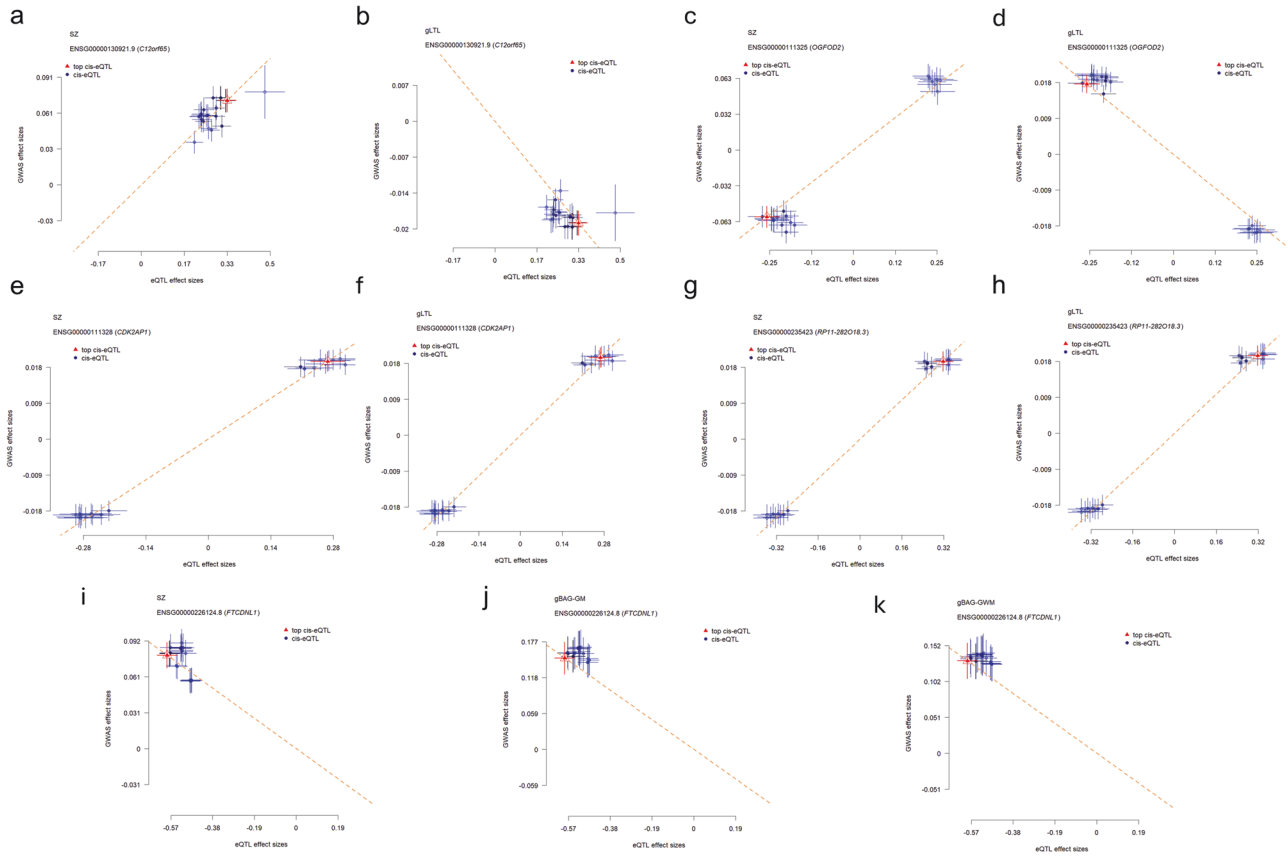


**Fig. 3 SMR effect plots for genes associated with SZ.** Plots of the effect size from GWAS against effect sizes from eQTL data for C12orf65 for SZ (**a**) and gLTL (**b**), OGFOD2 for SZ (**c**) and gLTL (**d**), CDK2AP1 for SZ (**e**) and gLTL (**f**), RP11-282O18.3 for SZ (**g**) and gLTL (**h**) and FTCDNL1 for SZ (**i**), gBAG-GM (**j**) and gBAG-GWM (**k**). Abbreviations: gBAG-GM, genetically predicted brain age gap gray matter; gBAG-GWM, genetically predicted brain age gap gray white matter; gLTL, genetically predicted leukocyte telomere length; SZ, schizophrenia.

transiently increased during severe physical stress, and to be sustained and accompanied by accelerated oxidation to inactive biopterin in individuals with depression [61]. In addition, serum biopterin levels have been shown to be lower in individuals with MDD and SZ compared with controls, while this deficit was not observed in individuals with BD compared with controls [62]. Folic acid deficiency and subsequent increase of homocysteine levels, that induces accumulation of DNA damage due to a methyl donor deficiency state, have been linked to increased risk of age-related disorders [63], while increased total homocysteine levels have been associated with faster rates of total brain volume loss during aging [64]. While a potential association between reduced serum folate levels and BD has been described [65], whether supplementation of folate might exert clinical benefits is not clear, with some studies showing a potential beneficial effect of adjunct treatment with folate in manic episodes [66, 67].

While we identified several genetic variants shared between aging biomarkers and specific mental disorders, we also identified nine genes (Table 2) including genetic variants significant for all mental disorders. Among cross-disorder genes, variants in *CNNM2* were associated with increased risk of all disorders and reduced gLTL (Table 2). This gene encodes a protein that plays a substantial role in magnesium homeostasis by mediating the epithelial transport and renal reabsorption of this ion [68]. Magnesium is essential for maintenance of DNA structure and cellular health span, due to its substantial role in a variety of biological processes [69]. In addition, it is essential for the maintenance of telomere structure and function and can also modulate the activity of the telomerase enzyme, which is the main enzyme able to counteract telomere shortening [70]. Interestingly, increased dietary magnesium intake has been associated with longer LTL in a study including 2200 individuals from the NHANES cohort [71], while hypomagnesemia is a common condition in older adults and has been suggested to be able to contribute to cognitive decline [70]. While to our knowledge no study has investigated the association between deficiency of this ion and TL or other markers of aging in individuals with mental disorders, our results support the need to further investigate this relationship.

Among cross-disorder genes containing variants shared between mental disorders and BAG measures, *FADS2* encodes Fatty Acid Desaturase 2, a member of the fatty acid desaturase family that plays a crucial role in regulating plasma lipid levels [72] and in the synthesis of long-chain polyunsaturated fatty acid (LC-PUFA) such as eicosapentaenoic acid and docosahexaenoic acid from essential fatty acids. Besides being key components of neuronal membranes and modulators of neuronal functions [73], PUFAs might be able to slow the age-related brain damage and cognitive decline in preclinical models [73] and could be associated with a lower rate of cognitive decline in humans [74], although interventional studies have yielded conflicting results [75]. Among cross-disorder genes part of the druggable genome based on DGIdb, *ASIC2* encodes a member of the degenerin/epithelial sodium channel (DEG/ENaC) superfamily suggested to play a role in neurotransmission [76]. The ASIC2 channel is also permeable to lithium, the mainstay in the treatment in BD, and the rs11869731 variant in this gene has been associated with lithium response in a study including 200 individuals of Sardinian origin with BD [77], though this variant was not significant at a genome-wide threshold in a larger GWAS on lithium response [78]. The mood stabilizer lithium has been suggested to exert a

counteractive effect on telomere shortening as well as potential anti-aging effects in multiple preclinical models [79], although negative results have also been reported [80]. The observation that genetic variants located in a channel permeable to lithium are shared between aging biomarkers and severe mental disorders provides additional support to the hypothesis of an interaction between lithium and aging hallmarks. However, these results have to be interpreted cautiously as there are still several open questions regarding the potential antiaging effects of lithium as regards to duration of treatment, formulation, as well as whether this effect could be exerted at doses lower than those required for its mood stabilizing properties [81].

The most robust result from two-sample MR was a significant bidirectional association between mvAge and MDD, as this was the only association significant also based on the sensitivity analysis conducted with MRlap. The functional analysis conducted with SMR identified genes whose genetically predicted expression levels were associated with both mental disorders and aging biomarkers. The most compelling result was the finding of reduced expression of *CRHR1* associated with reduced risk of MDD and BAG measures. This druggable gene encodes the corticotropin-releasing hormone receptor type 1, a key component of the hypothalamic–pituitary–adrenal axis. *CRHR1* activates signalling pathways involved in several processes implicated in depression such as synaptic plasticity, neuroinflammation, autophagy and gut dysbiosis [82]. Preclinical studies suggest a central role of *CRHR1* in stress-induced depressive phenotypes, with CRHR1 antagonists suggested to exert antidepressant effects in mice [83]. In addition, *CRHR1* was identified as a pleiotropic gene shared between Alzheimer's disease and frailty [84] and genetic variants in this gene have been previously reported to modulate aging effects on working memory [85], further supporting its potential role in MDD and accelerated aging.

To our knowledge, the present study was the first to quantify shared genetic heritability and identify pleiotropic genes associated with severe mental disorders and a comprehensive set of aging biomarkers, using a suite of state-of-the-art methods. While our results add to the scarce knowledge of shared genetic determinants between mental disorders and aging markers, they should be interpreted in light of several limitations. Firstly, while our study was focused on genetic factors, aging is a complex multifactorial process involving multiple interacting mechanisms, including environmental and lifestyle factors that have not been considered in this study. While analyses incorporating gEAA partly address this aspect, the specific role of environmental factors able to affect aging and their interaction with genetic factors might be the focus of expansion of this work. Secondly, our analyses only comprised participants of European ancestry, thus potentially restricting their generalizability to participants with a different origin. For some aging phenotypes we observed a mixed pattern of effect directions. This might lead to speculate that there might be subgroups of patients with severe mental disorders with different degrees of risk for genetically predicted aging phenotypes. Thirdly, while we included the largest GWAS summary statistics available for all traits, the different numbers of participants and power imbalance across cohorts might have at least partly affected our results. For instance, a limited number of shared loci as well as a poor fit of most MiXeR models were observed for the gEAA datasets, which included the lowest number of participants across aging markers. Thus, the data on gEAA should be treated as exploratory. Future studies are needed to further explore the potential cross-trait pleiotropy between mental disorders and these aging markers. Finally, while we conducted in-silico analyses to evaluate the functional effect of identified variants and functional enrichment of genes in which they are located, further investigation of the potential molecular mechanisms underlying the role of these genes in accelerated cellular aging, as well as validation in independent cohorts is required.

In conclusion, our findings support the existence of shared genetic loci between severe mental disorders and biomarkers of cellular aging and prioritize genes involved in synapses and in metabolic functions related to micronutrients for further investigation.

## DATA AVAILABILITY

Genome-wide association summary statistics used for all analyses are publicly available. GWAS summary statistics for BD, MDD and SZ can be downloaded from the PGC website at https://pgc.unc.edu/. Summary statistics for longevity (i.e. multivariate GWAS of aging, mvAge), can be downloaded at https://zenodo.org/record/7926323. Summary statistics for brain age gap measures are available via Zenodo (https://doi.org/10.5281/zenodo.14826943). GWAS summary statistics for LTL are available at https://figshare.com/s/caa99dc0f76d62990195, while statistics from mtDNA-cn can be downloaded from the GWAS catalogue (https://www.ebi.ac.uk/gwas/publications/35023831). GWAS summary statistics for EAA are available at https://datashare.is.ed.ac.uk/handle/10283/3645.

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## AUTHOR CONTRIBUTIONS

CP: Conceptualization, Formal Analysis, Funding Acquisition, Writing – Original Draft Preparation; MN: Conceptualization, Writing – Original Draft Preparation; MM: Writing – Review & Editing; AS: Writing – Review & Editing; TK: Conceptualization; Supervision; Writing – Review & Editing.

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## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. For all GWAS datasets, ethical approval was obtained by the local ethics committees of the original GWAS studies and informed consent was obtained from all participants. Additional ethical approval was not required as the present study involved secondary analysis of publicly available de-identified data.

## ADDITIONAL INFORMATION

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